Public Health Goal for
Endrin
In Drinking Water

Prepared by

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California Environmental Protection Agency

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PREFACE

Drinking Water Public Health Goals

Pesticide and Environmental Toxicology Section

Office of Environmental Health Hazard Assessment

California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (amended Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.
2. PHGs for carcinogens or other substances which can cause chronic disease shall be based solely on health effects without regard to cost impacts and shall be set at levels which OEHHA has determined do not pose any significant risk to health.
3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.
4. OEHHA shall consider the existence of groups in the population that are more susceptible to adverse effects of the contaminants than a normal healthy adult.
5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.
6. In cases of insufficient data to determine a level of no anticipated risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.
7. In cases where scientific evidence demonstrates that a safe dose-response threshold for a contaminant exists, then the PHG should be set at that threshold.
8. The PHG may be set at zero if necessary to satisfy the requirements listed above.
9. OEHHA shall consider exposure to contaminants in media other than drinking water, including food and air and the resulting body burden.
10. PHGs adopted by OEHHA shall be reviewed every five years and revised as necessary based on the availability of new scientific data.

PHGs adopted by OEHHA are for use by the California Department of Health Services (DHS) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs).

Whereas PHGs are to be based solely on scientific and public health considerations without regard to economic cost considerations, drinking water standards adopted by DHS are to consider economic factors and technical feasibility. Each standard adopted shall be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory in nature and represent only non-mandatory goals. By federal law, MCLs established by DHS must be at least as stringent as the federal MCL if one exists.

PHG documents are used to provide technical assistance to DHS, and they are also informative reference materials for federal, state and local public health officials and the public. While the PHGs are calculated for single chemicals only, they may, if the information is available, address hazards associated with the interactions of contaminants in mixtures. Further, PHGs are derived for drinking water only and are not to be utilized as target levels for the contamination of other environmental media.

Additional information on PHGs can be obtained at the OEHHA web site at www.oehha.ca.gov.

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PUBLIC HEALTH GOAL FOR ENDRIN IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.0018 mg/L (1.8 ppb) has been developed for endrin in drinking water. The PHG is based on the observation of seizures and minor pathological changes to the liver in dogs fed 2 and 4 ppm endrin for two years (Jolley et al., 1969). Dogs receiving 0.1, 0.5 or 1.0 ppm in the same study had no identifiable toxic changes at the conclusion of the experiment. Hence, the LOAEL for this study is 2 ppm and the NOAEL is 1.0 ppm. For the calculation of the PHG, the NOAEL of 1 ppm endrin is converted to a corresponding dose of 0.025 mg/kg-day, which is the estimated dose based on the amount of food consumed/day. The PHG calculation assumes an adult body weight of 70 kg and consumption of 2 L/day of drinking water, applying an uncertainty factor of 100 and assuming a 20% relative source contribution. Based on this calculation, OEHHA adopts a PHG of 0.0018 mg/L (1.8 ppb) for endrin in drinking water.

INTRODUCTION

The purpose of this document is to establish a PHG for endrin. In 1995, a Maximum Contaminant Level (MCL) of 0.002 mg/L was adopted by the California Department of Health Services (DHS) (CCR, 1998). This level is the same as the federal Maximum Contaminant Level Goal (MCLG) and MCL of 0.002 mg/L for endrin (U.S. EPA, 1990; 1992a). In 1993, OEHHA proposed a Recommended Public Health Goal (RPHG) of 0.002 mg/ml (OEHHA, 1993).

Due to concerns over its apparent hazards, U.S. EPA has prohibited the sale and distribution of endrin since 1986 (ATSDR, 1996). Although chemically related to aldrin and dieldrin, endrin was not deemed classifiable as to its carcinogenicity by the International Agency for Research on Cancer (IARC, 1987). U.S. EPA has classified endrin as group D, not classifiable as to its carcinogenic potential (IRIS, 1997).

In this document, we reevaluate the available data on the toxicity of endrin, primarily by the oral route, and include information available since previous assessments by U.S. EPA (1990), OEHHA (1993) and U.S. EPA (1992). To determine a public health-protective level of endrin in drinking water, sensitive groups are identified and considered, and relevant studies are identified, reviewed and evaluated.

CHEMICAL PROFILE

Chemical Identity

Endrin is an organochlorine alicyclic compound that also exists in the aldehyde and ketone forms. The chemical formula, structure, synonyms and identification numbers are listed in Table 1 and are adopted from ATSDR (1996).

Physical and Chemical Properties

Other important physical and chemical properties of endrin and its related products, endrin aldehyde and endrin ketone, are given in Table 2. Endrin is slightly soluble in water and has low volatility.

Production and Uses

Endrin, an insecticide, rodenticide and avicide, was first used in the United States in 1951. Pests controlled included cutworm, voles, grasshoppers, borers and others on various crops both in food and nonfood commodities. It was also used to control nuisance birds. Largely due to concerns over its toxicity to nontarget bird populations, some its uses were canceled by U.S. EPA in 1979 except for the control of infestation at bird perches. This latter use was finally canceled in 1991. Endrin can still be used in foreign countries, and potentially affected produce may be imported to the United States. However, both U.S. EPA and FDA revoked all food tolerances for endrin in 1993 (ATSDR, 1996).

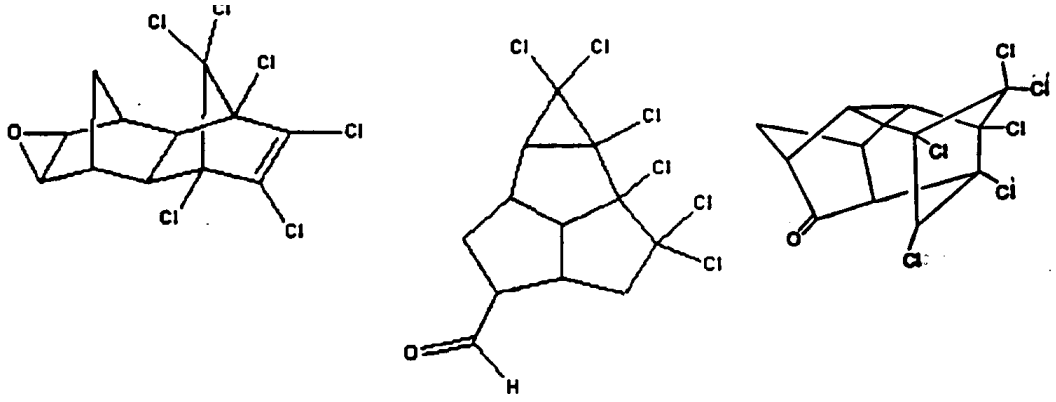
Endrin is closely related to the pesticides dieldrin and aldrin, whose registrations have been canceled as well. It is estimated that nearly 10 million pounds of endrin were sold in the United States in 1961. By 1971, production declined to less than a million pounds (ATSDR, 1996). At present it is difficult to determine whether endrin is still produced in the United States for export to foreign countries.

Sources

As mentioned above, endrin is no longer registered for use in the U.S., and levels in the environment appear to be declining. However, due to its persistence, endrin residues can be expected to be found in agricultural soils and in hazardous waste sites. Releases from these sites can continue to be sources of endrin exposure to humans.

Table 1. Chemical identity of endrin, endrin aldehyde and endrin ketone (ATSDR, 1996)[1]

Characteristic	Endrin	Endrin Aldehyde	Endrin Ketone
Chemical name	2,7:3,6-Dimethano-napth(2,3-b)oxirene, 3,4,5,6,6a,7,7a-octahydro-(1aα, 2β, 2aβ, 6aα,6aβ,7β, 7aα)	1,2,4-Methenocyclo penta(cd)-pentalene-5-carboxaldehyde, 2,2a,3,3,5,7-hexachlorodecahydro-(1aα, 2β, 2aβ, 4β,5β,6aα,6aβ,7R)	2,5,7-Methano-3H-cyclopenta(a)pentalen-3-one, 3b,4,5,6,6a-hexachlorodecahydro(2α, 3aβ, 3bβ, 4β, 5β, 6aβ,7α, 7aβ, 8R)
Synonyms(s)	Endrin;1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4A, 5,6,7,8,8A-octahyroendo, endo-1,4:5,8-dimethanonapththalene, and others	Endrin aldehyde:1,24-methanecyclopenta(c,d)pen talene-5-carboxadehyde, 2,2a3,3,5,7-hexachlorodecahydro	Endrin ketone
Registered trade names(s)	Mendrin, Hexadrin, Endrex, experimental insecticide 269	No data	Delta-keto 153
Chemical formula	$C_{12}H_8Cl_6O$	$C_{12}H_8Cl_6O$	$C_{12}H_8Cl_6O$
Identification numbers:	72-20-8	7421-93-4	53494-70-5
CAS registry	IO1575000	PC8580000	PC8600000
NIOSH RTECS	P051; D012	No data	No data
EPA hazardous waste	7216522	8300215	No data
OHM/TADS	UN 2761; NA 2761; IMO 6.1	UN 2761; IMO 6.1	UN 2811; NA 2761; IMO 6.1
DOT/UN/NA/IMCO ship.			
	198	6181	No data
HSDB	01565	No data	No data
NCI	C00157		
Structure			



1. CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Dept. of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Base; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 2. Chemical and physical properties of endrin, endrin aldehyde and endrin ketone

Characteristic	Endrin	Endrin Aldehyde	Endrin Ketone
Molecular weight	380.9	381.9	380.9
Color	White Colorless	No data	No data
Physical state	Crystalline solid	Solid	Solid
Melting Point	235 °C 226 - 230 °C (decomp.)C	145 - 149 °C (decomp.)	No data
Boiling Point	Decomposes at 245 °C Decomposes above 200 °C	No data	No data
Density at 20 °C	No data	No data	No data
Specific Gravity	1.7 at 20 °C	No data	No data
Odor	Mild; odorless	No data	No data
Odor Threshold		No data	No data
Water Air	0.041 mg/L 1.8×10^{-2} ppm		
Solubility			
Water at 25 °C Organic solvents	200 µg/L acetone 17 g/100 mL benzene 13.8 g/100 mL carbon tet. 3.3 g/100 mL hexane 7.1 g/100 mL xylene 18.3 g/100 mL	50 mg/L, 0.25 - 0.26 ppm No data	No data No data
Partition coefficients: Log K_{ow} Log K_{oc}	5.6, 5.34 (calculated) 5.45 (calculated) 4.532 (calculated) 5.195 (±0.005)	3.146, 4.7, 5.6 (calculated) 4.80 (calculated) 3.929 - 4.653 (calculated)	4.99 (calculated) No data
Vapor pressure at 25 °C	2.0×10^{-7} mm Hg	2.0×10^{-7} mm Hg	No data
Henryś law constant	4.0×10^{-7} atm-m^3/mol (calculated) 5.41×10^{-7} atm-m^3/mol	2×10^{-9} atm-m^3/mol 2.9×10^{-9} atm-m^3/mol 3.67×10^{-8} atm-m^3/mol	2.02×10^{-8} atm-m^3/mol

Characteristic	Endrin	Endrin Aldehyde	Endrin Ketone
	(calculated)	(calculated)	(calculated)
Autoignition temperature	No data	No data	No data
Flashpoint	Non-flammable	Non-flammable	No data
Flammability limits	No data	No data	No data
Explosive limits	No data	No data	No data
Conversion factors	1 ppm = 15.6 mg/m^3 1 mg/m^3 = 0.006 ppm	1 ppm = 15.6 mg/m^3 1 mg/m^3 = 0.006 ppm	1 ppm = 15.6 mg/m^3 1 mg/m^3 = 0.006 ppm

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Since all uses of endrin in the U.S. have been canceled, no significant releases into the environment are expected. Rather, occurrences of endrin in various environmental media are entirely due to previous uses of endrin and its persistence.

Air

Although endrin has low volatility, significant releases of endrin were detected in the air several days after ground application. Once in the air, endrin is transformed by heat to endrin ketone, with small amounts of endrin aldehyde. In turn, endrin aldehyde and endrin ketone react photochemically with hydroxyl radicals in the atmosphere. The half life of endrin aldehyde and endrin ketone is only a few days (ATSDR, 1996).

Endrin was found at higher concentrations in the air around manufacturing facilities during its manufacture. It was almost never found in urban areas where it was rarely used. Endrin was detected in 4 of 102 National Priority List (NPL) sites, where it was already present in the soils (ATSDR, 1996).

Soil

Endrin does not appear to be significantly degraded in soils. In one study, about 41% of applied endrin remained in a field after 14 years (Nash and Woolson, 1967). It is hydrophobic and thus adsorbs strongly to soil particles and tends to be immobile, based on an estimated K_{oc} of 34,000 (ATSDR, 1996). However, very little information is available about the environmental transport and partitioning of endrin into the various media.

Endrin has been detected in cropland soils in several states including California, Alabama, Georgia, Illinois, Arkansas, Louisiana, New York, New Jersey, Nebraska, North Carolina, Florida and others (ATSDR, 1996).

Water

Endrin is very insoluble in water; endrin ketone and aldehyde, slightly more so. Detections of endrin in ground and surface waters are rare; however, endrin is detected in surface water and leachate samples taken from NPL sites. Endrin, once in water, strongly adsorbs to sediment, thereby removing the chemical from the water and concentrating it in the sediment (ATSDR, 1996).

In a water quality monitoring program conducted by the California Department of Health Services, endrin was detected in 2 out of 5,109 public drinking water sources sampled from 1984 to 1992, at mean and maximum concentrations of 0.06 and 0.10 ppb, respectively (Storm 1994). None of the samples exceeded the MCL of 2 ppb. In ground water surveys conducted by the California Department of Pesticide Regulation from July 1, 1995 to June 30, 1996, endrin was not detected in water (DPR, 1996).

Food

In contrast to its persistence in soils, endrin on soil and plant surfaces is likely to decrease as it is more susceptible to volatilization, photodegradation and heat transformation. However, uptake of endrin by plants was noted from soils treated as long as 16 years after planting (Nash and Harris, 1973).

Endrin has been reported in food commodities by monitoring programs conducted by various agencies. In Canada, endrin was detected in below and above ground vegetables, as well as in milk, but not in meat products (ATSDR, 1996). Endrin was detected in FDA's Pesticide Residue Monitoring Program (for the period of 1990-1995). Although no endrin concentrations were reported, less than 1% of the samples exceeded the tolerance for endrin. In FDA's Total Diet Studies, endrin was detected yearly from 1987 to 1991 (except for 1990) (ATSDR, 1996).

Of concern is the significant potential for endrin to bioaccumulate and bioconcentrate in aquatic organisms. Endrin runoff from agricultural fields or discharge by industrial plants is the principal source of endrin in estuaries. In the National Contaminant Biomonitoring Program, maximum endrin concentrations in whole fish in the United States for the periods 1976-77, 1978-79, 1980-1981, and 1984 were 0.4, 0.11, 0.30 and 0.22 ppm, respectively. Corresponding geometric means were less than 0.01 ppm (Schmitt *et al.*; 1985, 1990). In the 1986 National Study of Chemical Residues in Fish conducted by the EPA, endrin was detected in fish tissue samples at 11% of 362 sites surveyed, with a maximum concentration of 0.162 ppm and a mean of 0.002 ppm (EPA, 1992b). No detectable endrin was reported in a 1994 FDA survey of important aquacultural derived species such as catfish, crayfish, shrimp, trout, salmon, and oysters. This result is important since many impoundments are located on former agricultural land that could be contaminated with endrin.

The FDA has concluded that endrin is no longer present in the environment to the extent that it may be contaminating food or feed at levels of regulatory concern (USDA, 1995).

Other Sources

No other sources of endrin were identified.

METABOLISM AND PHARMACOKINETICS

Absorption

Endrin appears to be well absorbed through all routes of exposure, although insufficient information exists on the rate and extent of this absorption. From experimental animal studies performed by Treon and colleagues (1955) it is apparent that endrin is absorbed by inhalation and through the skin. Occupational poisonings have been presumed to be the result of endrin inhalation, but there was probably dermal absorption as well (Hoogendam *et al*., 1962).

Metabolism

In Figure 1, a summary of the known pathways of endrin metabolism is presented. Although there is some species variation, in most cases, the methylene bridge of endrin (I) is attacked preferentially to form mostly anti-(product II) and lesser amounts of the syn-(product III) hydroxyendrin. The other vulnerable position is the C-3, which is hydrolyzed to Product IV. The epoxide appears to be less vulnerable to attack as the pathway yielding product V is minor (Hutson, 1981). Products II and III may be conjugated with sulfates and eliminated. However, dehydrogenation of Products II and III by microsomal oxidases leads to the production of 12-ketoendrin (product VI), found in rat tissues, which is thought to be the toxic metabolite (Baldwin *et al.*, 1970; Hutson, 1981).

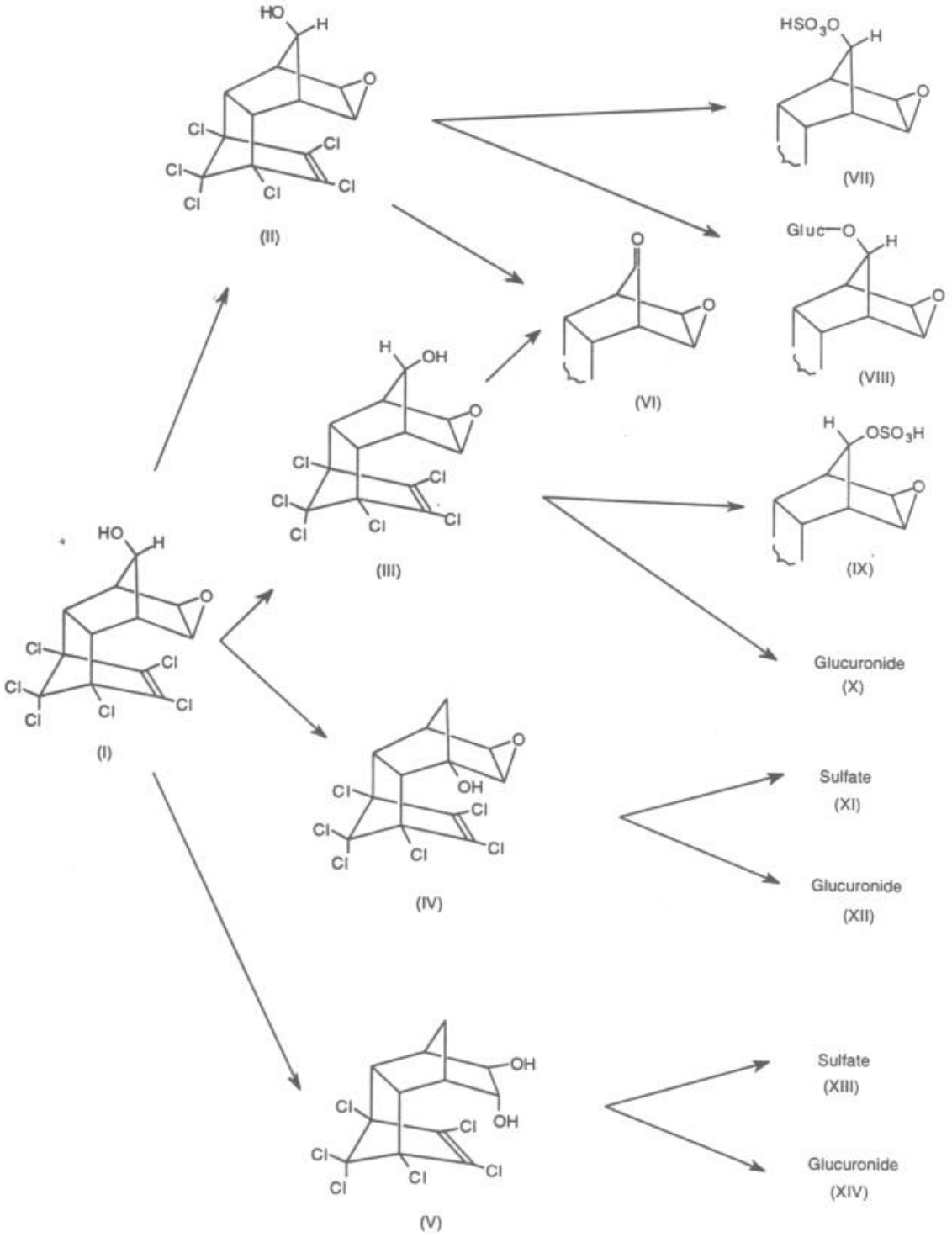
Distribution

After absorption, endrin tends to bioaccumulate in fat. In a study measuring deposition of endrin (Hutson *et al.*, 1975), rats were given an oral dose of 2.5 mg/kg of radiolabeled endrin and sacrificed on the third day. The distribution of the dose in males was as follows: 1.2% in liver, 0.6% in kidney, 1.7% in fat, 2.3% in skin and 12.2% in carcass. Female rats had 2% in the liver, 0.35% in kidney, 8% in fat, 4% in skin and 28.2% in the carcass. In Beagle dogs (Quick *et al*., 1989) who died upon ingesting bait containing endrin, the highest tissue concentrations were found in the fat, followed by the liver and brain with the lowest concentrations found in lung and muscle. In experimentally treated dogs (Richardson *et al.*, 1967), endrin was given in the feed at an estimated dose of 0.1 mg/kg/day for 128 days. Upon sacrifice endrin concentrations were highest in the fat (250-760 ppb), followed by muscle (120-310 ppb), heart (125-170 ppb), pancreas (87-280), liver, kidney and lung (<100ppb). Levels in the blood were 1-8 ppb and remained constant during the duration of dosing.

Endrin appears to readily pass through the placental barrier. Endrin and 12-ketoendrin were detected in the maternal liver and fetal tissues of rats and hamsters administered endrin during gestation (Chernoff *et al.*, 1979; Kavlack *et al*., 1981). Fetal tissue concentrations of endrin metabolites ranged from 2 to 8% that of maternal livers.

Workers at an endrin manufacturing plant in England, exposed primarily by inhalation, had no detectable anti-hydroxyendrin or 12-ketoendrin in their blood (Baldwin and Hutson, 1980). However, 12-ketoendrin, anti-12-hydroxyendrin and its β-glucuronide were detected in both the feces and urine.

Figure 1. Proposed metabolism of endrin (ATSDR, 1996)



Endrin is metabolized by four pathways. In the major pathway, endrin is oxidized at the methylene bridge to yield Products II and III, which then can be metabolized to product VI. In the minor pathways, either the epoxide is hydrolyzed (Product V) or the C-3 position is hydrolyzed (Product IV). All products appear to be conjugated by sulfate or glucuronide before elimination, except for Product VI.

Excretion

Endrin has been detected in the feces and urine of experimentally treated animals as well. In rats, 55-75% of ^{14}C-endrin was metabolized to mostly the glucuronide of anti-hydroxyendrin within 24 hours upon dosing with 0.5-2.5 mg/kg (Hutson *et al.*, 1975). Male rats eliminated 69% of the label within 3 days, females eliminated 45%.

In workers from an endrin manufacturing plant, anti-12-hydroxyendrin and 12- ketoendrin were detected in the feces, and the glucuronide conjugate of 12-ketoendrin were detected in the urine (Baldwin and Hutson, 1980).

Endrin has an estimated half-life of 2-6 days both in humans and in animals. Thus it is not likely to accumulate in tissues like dieldrin (Ert and Sullivan, 1992)

TOXICOLOGY

Toxicological Effects in Animals

Acute Toxicity

A cat, exposed twice for one hour to 6,500 mg/m^3 endrin (417 ppm) as a spray of 1.5% aqueous solution, died within 24 hours (Ressang *et al*., 1959). In the same study another cat died within 24 hours of receiving a single oral dose of 6 mg/kg body weight of endrin. Oral LD_{50}s were calculated to be 7.3 and 16.8 mg/kg for 6-month-old and one-month-old female rats, respectively, and 43.4 and 28.8 mg/kg for male rats, respectively (Treon *et al*., 1955). Similarly, in guinea pig females were more sensitive with oral LD_{50}s of 36 mg/kg for males and 16 mg/kg for females (Treon *et al*., 1955).

Subchronic Toxicity

Treon and colleagues (1955) treated six species of animals with sublimed endrin vapor at 15 mg/m^3 (0.36 ppm) for 7 hours per day (--one exposure), 5 days a week for up to 130 exposures. Two of 4 rabbits died after 26 and 90 exposures and 1 out of 3 mice died after 22 exposures. The cat, 2 guinea pigs, 2 hamsters, and 4 rats survived 130 exposures. Diffuse degenerative changes were observed in kidneys, livers, and brains in all animals that died except in the mouse where effects on the brain were not noted. The two surviving rabbits developed granulomatous pneumonitis, while the other surviving species were not effected.

In the same study (Treon *et al*., 1955), five rabbits were given 1 mg/kg of endrin orally for 5 days per week for 10 weeks. Four of the five rabbits died during exposure, one each after 2, 30, 35 and 50 doses, while the fifth rabbit survived the experiment. Three weanling and three mature rats survived this level of dosage, but one out of three died when the dose was 2 mg/kg. The rabbits were reported to have abdominal extension, while the rats had developed hypersensitivity to stimuli. Dogs of both sexes (1-2/sex/dose) administered endrin in feed for 18 days to approximately 19 months had increased mortality at doses of 0.20-0.27 mg/kg-day (5 ppm) or greater, but animals survived doses of 0.15-0.21 mg/kg-day (4 ppm).

Male Sprague Dawley rats were administered endrin (3.5 mg/kg-day) by gavage for 5 days/week for periods ranging from 1 week to 7 months (Speck and Maaske, 1958). After one week of exposure, 4/30 animals died. Surviving animals exhibited an elevated respiration rate, excitability or irritability, and were predisposed to convulsions following auditory stimulation. Irregular EEG recordings were also observed following one week of exposure, but did not increase with number of exposures. Livers appeared spotty with zones of basophilic cells around the central and portal veins, suggesting some degenerative changes.

Genetic Toxicity

Endrin was not mutagenic in several mutagenicity assays including S. typhimurium with and without activation (Zeigler *et al*., 1987), mouse lymphoma cell assay (McGregor *et al*., 1991), unscheduled DNA synthesis or repair in rat, mouse, and hamster hepatocytes (Maslansky and Williams, 1981; Probst *et al*., 1981; Williams, 1980) and in sister chromatid exchanges (Sobti *et al*., 1983). No *in vivo* studies have been conducted with endrin. Chromosomal aberrations were observed in testicular cells of rats, but only upon intratesticular injection (Dikshith and Datta, 1973).

Developmental and Reproductive Toxicity

Developmental effects were observed in hamsters and mice, but less clearly in rats. Golden Syrian hamsters were treated on Gestation Day 7, 8, 9 with 5 mg/kg endrin (half of the LD_{50} as determined in this study). Significant increases in open-eye and webfoot occurred only in fetuses of mothers treated on Day 8 with endrin (Ottolengi *et al*., 1974). In another study hamsters treated on day 8 with 5 mg/kg had a significant occurrence of meningio-encephaloceles and fused ribs in their offspring (Chernoff *et al.*, 1979). In mice, exposure to 2.5 mg/kg on gestation day 9 resulted in significantly increased incidence of open-eye and cleft palate (Ottolenghi *et al*., 1974). In contrast, no dose-related evidence of open-eye and cleft palate were observed in mice intubated with 1.5 mg/kg-day endrin on gestation days 7-17 (Kavlock *et al*., 1981). The higher dose of 7 or 9 mg/kg endrin on gestation day 8 resulted in exencephaly (2 of one litter) and fused ribs (Kavlock *et al*., 1985). It should be noted that the control group had two cases of exencephaly in two litters. No developmental effects were noted in rats exposed to 0.45 mg/kg-day of endrin on gestation days 7-20 (Kavlock *et al*., 1981).

In a 3-generation reproduction study, weanling rats were fed at 0, 0.1, 1 or 2 ppm endrin in their diets (0.0, 0.005, 0.05 and 0.1 mg/kg-day, respectively) (Eisenlord *et al*., 1968). There were no effects on indices of fertility, gestation, viability or lactation. The number of pups in the F_{3A} generation was significantly increased relative to controls. There was higher mortality in the control group perhaps due to viral pneumonia. Survival information is therefore, compromised by the presence of viral pneumonia.

In a single generation reproduction study, groups of three female Beagle dogs were administered 0, 0.1, 0.5, or 2 ppm endrin (0.0, 0.03, 0.014, or 0.059 mg/kg-day, respectively) in the feed and mated with endrin-treated males from a concurrent chronic toxicity study (Kettering, 1971). Four treated females (one each from the low and middle dose groups and 2 from the high dose group) never accepted a male, and despite artificial insemination, did not become pregnant. Exploratory laparotomies, necropsies and microscopic examination of ovaries and uteri at termination of these dogs revealed no specific changes due to endrin. Because of the low number of animals per study group, it is difficult to conclude an effect on reproduction.

Teratogenic effects of endrin were evaluated in DBA/2J and C57BL/6J mice and compared with the effects of lindane and TCDD in C57BL/6J mice (Hassoun and Stohs, 1996). Endrin was given at 4.5 and 6 mg/kg-bw orally by gastric intubation on day 12 of gestation and animals were sacrificed on day 18. In the DBA/2 mice, significant reduction was noted in fetal weight at both doses and placental weight at the high dose. In the C57BL/6J mice, endrin produced significant decreases in fetal weight, fetal thymic weight and placental weight at both doses. Endrin caused about 25% maternal mortality in both strains at the higher dose, but no increase in number of terata was noted over controls.

Endrin has been recently classified as a reproductive toxicant under Proposition 65 (OEHHA, 1998)

Immunotoxicity

The only information directly related to immunity is found in the series of studies performed by Bagchi *et al*. (1992a,b). Time and dose-related increases in spleen-to-body weight ratios were observed in rats administered a single oral dose of 1.5-6 mg endrin/kg bw. At the same time, relative thymus weights were decreased.

No effects were reported on spleen weights of male and female Beagle dogs given 0.025-0.075 mg/kg-day of endrin in their diet for periods of 16.5-18.7 months (Treon *et al*., 1955).

Neurotoxicity

Neurotoxic effects from endrin exposure are described in detail in the Chronic Toxicity and Human Toxicity sections.

The ability to produce convulsions by endrin is shared with other polychlorocycloalkane pesticides. Convulsions are thought to be related to the inhibition of γ-amino butyric acid (GABA)-mediated functions in the CNS, particularly chloride ion transport. Binding of endrin or endrin metabolites to the GABA receptors may therefore be involved in the mechanism of convulsions (U.S. EPA, 1992c), however the specific mechanism is unknown at this time. Convulsions induced by endrin are treatable with succinylcholine.

Hepatotoxicity

It has been suggested that endrin toxicity may be due in part to oxidative stress associated with increased lipid peroxidation, decreased glutathione content and inhibition of glutathione peroxidase activity. Hassan and colleagues (1991) gave a single dose of 4 mg/kg of endrin each to rats, mice, guinea pigs and hamsters and sacrificed these animals 24 hours later. The investigators noted degenerative changes in the liver and kidneys of these animals. These changes were prevented by pretreating endrin-exposed animals with various antioxidants, suggesting that endrin was initiating lipid peroxidation.

Chronic Toxicity/Carcinogenicity

In the study of Treon *et al*. (1955), groups of 20 male and female Carworth rats, 28 days of age, were given 1, 5, 25, 50 and 100 ppm endrin through the diet. By the 80th and through the 106th week, statistically significant increases in deaths occurred in the 25 ppm and higher female dose

groups, and at the 50 ppm and higher level in males. Rats fed for 2 years at the 5 and 25 ppm level had higher liver-to-bodyweight ratios. This effect was not seen at lower doses. In addition, hypersensitivity and convulsions were noted in rats receiving 50 ppm and higher, but not in the lower doses.

In the same study (Treon *et al*., 1955) dogs (3-4 per group) were exposed to endrin at various concentrations in the diet. Dogs which received endrin at levels higher than 4 ppm died within two months. The remaining dogs were maintained at levels of 3 or 1 ppm for 84 weeks. All dogs survived at these levels and the only significant finding was enlargement of the kidneys and hearts at the 3 ppm level. Therefore, a NOAEL of 1 ppm can be assigned to this study, and this corresponds to a dose of 0.045-0.120 mg/kg-day (US EPA, 1992c).

Osborne-Mendel rats (50/sex/dose group), were exposed to 0, 1, 3, and 5 ppm endrin in feed for 10 weeks and then 0, 2, 6 or 12 ppm endrin for an additional 106 weeks (Deichman *et al*., 1970). Concurrently, rats were also exposed to aldrin and dieldrin. Tremors and convulsions were seen in females at all doses. There was no increased rate of tumors over controls noted in any dosed population, however, only liver, lungs and kidney tissues were examined microscopically.

A National Cancer Institute bioassay (NCI, 1978) was conducted by administering time-weighted average doses of 1.6-5 ppm endrin in feed to B6C3F_1 mice and 2.5-6 ppm in feed to 50 Osborne-Mendel rats for 80 weeks. Animals were observed for 31 or 34 weeks. Isolated cases of significantly increased tumors were reported, however, only adrenal carcinomas/adenomas in high dose male rats exhibited a dose-related trend. NCI concluded that these increases were not attributable to endrin exposure. The mean survival of high-dose male mice at the end of the study was markedly lower than that of the controls, while both low and high-dose females had survival rates similar to that of controls. Accidental increases in endrin dose given to low dose males precluded an evaluation of survival. No differences in survival rates were noted among the rat groups. The only clinical manifestation was signs of hyperexcitability in mice. No differences in body weight were noted.

Beagle dogs, 3-7 per group, were administered 0, 0.1, 0.5, 1.0, 2.0 or 4.0 ppm in the diet for two years (Jolley et al., 1969). Female dogs had observable seizures (evidence of convulsions) at doses of 2.0 and 4.0 ppm. Occurrences of slightly increased relative liver weights and mild histopathological effects in the liver were also noted at the two highest doses. No adverse effects on these parameters or on growth, food consumption, behavior, serum chemistry, urine chemistry or histological appearance of major organs occurred at 1 ppm. Therefore, a NOAEL of 1 ppm is identified which can be converted to a dose of 0.025 mg/kg based on a standard food factor of 2.5% bw/day (IRIS, 1997). These findings affirm the effects of endrin in dogs noted in the Treon (1955) study. Both studies were conducted in the same facility.

Toxicological Effects in Humans

Dutch pesticide plant workers exposed to endrin, primarily by inhalation, received levels which were high enough to cause tonic-clonic contractions and seizures, but no increase in deaths were reported in workers attributable to endrin exposure (Hoogendam *et al*., 1962; 1965). All workers who had convulsions showed specific anomalies in their electroencephalograms (EEGs) which persisted after the convulsions had ceased. A follow-up study of mortality was conducted on a subpopulation of workers who had at least four years of exposure (Ribbens, 1985). Total mortality among these workers was lower than expected for the population of Dutch men, and cancer-related deaths were also lower than expected.

In a retrospective cohort mortality study in U.S. aldrin/dieldrin/endrin manufacturing facilities, standardized mortality ratios were calculated for 2100 workers in two plants (Ditraglia *et al*., 1981). An increase in deaths due to nonmalignant respiratory disease in an aldrin/dieldrin/endrin cohort was observed at one plant. Total mortality and deaths due to neoplasms were lower than expected when compared with a normal population. The results could be due to a healthy worker effect. Slight increases in the incidences of cancer of the esophagus, liver, rectum, the lymphatic and hematopoietic system were noted at one plant, however these were not statistically significant. Because exposures did not include endrin exclusively, it is difficult to associate the increase in cancer rates to endrin. Furthermore, there was no observed increase in cancer-associated death rates in another plant that predominantly manufactured endrin (Ditraglia *et al*., 1981).

The first reported instance of endrin poisoning was in Wales where sacks of flour were contaminated by endrin spilled on the floor of a railway car. About 60 cases of acute poisoning were reported. Concentrations of 200-5,500 ppm endrin were detected in flour and 150 ppm in bread prepared with contaminated flour (Davies and Lewis, 1956). Based on this episode, a dose of 0.2-0.25 mg/kg-bw was estimated to be the dose sufficient to cause convulsions (Hays, 1963).

Accidental poisonings with flour contaminated with endrin have been also reported in Doha, Qatar and Hofuf, Saudi Arabia. About 874 people were hospitalized after acute exposure to endrin-contaminated flour which resulted in at least 26 deaths (Weeks, 1967). Initial signs included convulsions, headache, nausea and vomiting followed by death within 12 hours of the onset of these symptoms. Estimated ingested concentrations ranged from 48 to 1807 ppm (Curley *et al*., 1970).

In one reported case of endrin poisoning in the United States, five individuals suffered seizures as a result of ingesting endrin-contaminated taquitos; three of the individuals were from the same family (Waller *et al.*, 1992). Analysis of leftover taquitos from the affected family showed that endrin was confined to the tortilla shell with concentrations ranging from 2.4 to 4.6 ppm. No endrin was found in other taquitos of the same brand returned by consumers. These consumers also did not report any symptoms.

Several intentional poisonings have been reported as well. A 49-year-old man ingested 12 grams of endrin (dissolved in aromatic hydrocarbons) (Runhaar *et al*., 1985). Convulsions persisted for 4 days and death occurred in 11 days. In 11 other cases, death occurred between 1-6 hours, however doses were not estimated.

In less severe poisonings by endrin, patients complain of dizziness, weakness, nausea and abdominal discomfort. Occasionally insomnia and vomiting and more rarely, slight disorientation, aggressiveness, and temporary deafness occurred. Acute poisoning cases exhibit sudden epileptic convulsions with a duration of several minutes. Convulsions can be violent, sometimes resulting in head injuries or shoulder dislocations. A semiconscious state may follow which can last up to half an hour. Vomiting sometimes occurs later, and weakness, lethargy, and headaches may persist for days to weeks. Recovery is generally complete with the exception that with severe poisonings, convulsions may produce anoxia resulting in residual damage to the CNS (Coble *et al*, 1967).

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

Chronic studies on endrin toxicity are limited to a few rodent and dog studies. The most sensitive species appears to be the dog (with a LOAEL being about 10 times less than that observed in the rat). Furthermore, the dog studies indicate neurologic and hepatic effects which are characteristic of endrin exposures in animals and humans. Therefore candidate studies for PHG development include those of Treon et al. (1955) and Jolley et al. (1969) which employed long-term exposure to dogs.

The NOAEL for both studies was 1 ppm, however it is difficult to estimate the dose because the actual food consumption by dogs is not known. U.S. EPA estimates that from the Treon et al. (1955) study, the dose ranges from 0.045-0.12 mg/kg-day (US EPA, 1990), while in the Jolley et al. (1969) study, the NOAEL was estimated to be 0.025 mg/kg-day. U.S. EPA has selected 0.025 mg/kg-day as the dose representing the NOAEL for MCL calculation (US EPA, 1990; 1992c). Although the Treon (1955) NOAEL of 0.045 mg/kg-day is higher than the Jolley et al. (1969) NOAEL of 0.025 mg/kg-day in dose, the U.S. EPA (1990) feels that the dose from the Treon et al. (1955) study is unusually high, so it defers to using the dose estimate from the Jolley et al. (1969) study. The Jolley et al. (1969) study is preferred to the Treon (1955) study also for the reason that there is a higher degree of confidence in the results. The Jolley et al. (1969) study appears to be conducted in accordance with better standards, with a greater number of dogs studied for a longer duration.

Numerous cases of endrin poisoning have been reported in humans, however it has been difficult to estimate effective doses for these cases. The closest estimate of a minimum dose leading to human seizures was 0.2-0.25 mg/kg as provided by Hays (1963) for the Wales poisoning episode.

Carcinogenic Effects

Endrin was not mutagenic in bacteria, but did produce chromosomal aberrations. Endrin is also structurally similar to aldrin, dieldrin, chlordane and heptachlor, all proven animal carcinogens. However, at present there is no evidence to characterize endrin as a carcinogen. Epidemiologic studies do not suggest an increase in cancer rates with endrin exposed workers, but also cannot demonstrate that endrin is not associated with cancer. These studies are either inadequate or are compromised by the fact that workers were exposed to other pesticides besides endrin. Even so, these other pesticides were usually aldrin, dieldrin, and others related to endrin and are confirmed animal carcinogens.

Similarly, no evidence for an increase in tumor incidence was seen in four animal bioassays conducted with endrin. However, there were deficiencies reported in some of these studies, and others are rather dated, thereby not conducted in accordance with present day standards.

CALCULATION OF PHG

Noncarcinogenic Effects

Calculation of a public health-protective concentration (C, in mg/L) for endrin in drinking water for noncarcinogenic endpoints follows the general equation:

$$C = \frac{NOAEL/LOAEL \times BW \times RSC}{UF \times L/day}$$

where,

NOAEL/LOAEL	=	No-observed-adverse-effect-level or lowest-observed-adverse-effect-level
BW	=	Adult body weight (a default of 70 kg for male or 60 kg for female)
RSC	=	Relative source contribution (a default of 20% to 80%)
UF	=	Uncertainty factors (typical defaults of a 10 to account for inter-species extrapolation, and a 10 for potentially sensitive human subpopulations)
L/day	=	Adult daily water consumption rate (a default of 2 L/day)

The NOAEL is derived from a chronic dog exposure study in which seizures and minor pathologic changes to the liver were observed in dogs fed 2 and 4 ppm endrin for two years (Jolley et al., 1969). Dogs receiving 0.1, 0.5 or 1.0 ppm in the same study had no identifiable toxic changes at the conclusion of the experiment. Hence, the LOAEL for this study is 2 ppm and the NOAEL is 1.0 ppm, with the dose equivalent of 0.025 mg/kg bw-day:

$$C = \frac{0.025\ mg/kg\text{-}day \times 70\ kg \times 0.2}{100 \times 2L/day}$$

$$C = 0.0018\ mg/L \text{ or } 1.8\ ppb$$

A relative source contribution factor of 0.2 was selected with the understanding that endrin is still present in the environment, but in diminishing quantities. More endrin exposure can be expected from food than from water as quantifiable amounts of endrin remain in soils and sediments. No contribution is expected from air.

Based on this calculation, the PHG for endrin is 1.8 ppb.

Carcinogenic Effects

At present there is no evidence to characterize endrin as a carcinogen.

RISK CHARACTERIZATION

The PHG for endrin is based on a chronic dog study completed in 1969. The study defines a NOAEL based on absence of convulsions and liver changes in the 1 ppm dose group which occurred at the 2 ppm dose group (LOAEL). Convulsions are a sensitive sign of the neurological effects due to endrin. It is clear that the dog is more sensitive to the neurologic effects of endrin than rodents. This NOAEL is supported by similar results presented by the same laboratory fifteen years earlier, where the NOAEL was also 1 ppm. The difference between the two NOAELs lies in deriving the dose estimate, since the actual administered concentration is the same.

Certainty in the PHG is complicated by the fact that the most relevant studies for critical dose estimation were not performed and characterized in ways meeting present day standards. Specific histological and clinical chemistry evaluations are lacking and therefore the possibility exists that more sensitive effects have not been detected. A limited number of dogs was used per group in the Treon et al. (1955) and Jolley et al. (1969) studies. Overall, low to medium confidence can be assigned to the selection of the critical study.

In the calculation of the PHG, standard assumptions were used which include the interspecies dose factor, which assumes that humans would be more sensitive than dogs. From human poisoning-case reports, it is possible to conclude that humans could have convulsions at doses below those that produced the same effect in dogs. Therefore, use of the intraspecies and interspecies factors, resulting in a total factor of 100, should provide an adequate margin of safety.

The source contribution factor of 20% is likely to overstate the risk from endrin exposure from water. Endrin is no longer registered for use in the U.S. and is strictly controlled for under the basis of zero tolerance in food. It can still be present in the environment, albeit in ever diminishing quantities. However, endrin has been involved in food poisoning cases in the U.S., years after registration has ceased. Therefore, for public health safety concerns it should be assumed that endrin exposure is going to be primarily from sources other than drinking water.

OTHER REFERENCE VALUES AND REGULATORY STANDARDS

ATSDR has derived an intermediate oral MRL (Minimum Risk Level) of 0.002 mg/kg-day based on the laboratory study in dogs showing neurotoxic effects (Treon *et al*., 1955). A chronic oral MRL of 0.0003 mg/kg-day was derived based on the Jolley et al. (1969) study. Similarly the U.S. EPA had derived a reference dose for endrin which is identical to that of the ATSDR chronic oral MRL and is based on the same study and assumptions (IRIS, 1997). EPA has also declared that endrin is not classifiable as to its carcinogenicity (category D) (IRIS, 1997). The National Toxicology Program has assigned endrin the carcinogen code N (negative) (ATSDR, 1996).

The U.S. EPA has also established an ambient water quality criterion for the protection of human health as 0.001 mg/L, and for the protection of freshwater and saltwater aquatic life as 0.0023 µg/L (U.S. EPA, 1992c).

As part of Phase V of primary drinking water regulations mandated by the 1986 Amendment of the Safe Drinking Water Act (SDWA), U.S. EPA (1990) proposed the MCL for endrin to be 0.002 mg/L. In responding to public comments, U.S. EPA (1992) confirmed the proposed MCL. The California DHS adopted the same MCL for endrin as 0.002 mg/L (2 ppb) in 1995 (CCR, 1998) based on a recommended public health level of the same value from OEHHA (1993).

The PHG developed here is essentially the same as U.S. EPAš MCL and Californiaš MCL. The difference lies only in that the PHG is not rounded to one significant figure.

Endrin has been recently classified as a reproductive toxicant under Proposition 65 (OEHHA, 1998).

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